EPINEPHRINE AND NOREPINEPHRINE RELEASE IN THE FETUS AFTER REPEATED HYPOXIA

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Repetitive hypoxic stress induced by labor is a powerful stimulus for catecholamine release in the fetus. Clinical investigations and animal experiments have shown that repeated hypoxia is accompanied by typical alterations of the fetal heart rate(FHR) and increasing Epinephrine (E) as well as Norepinephrine (NE) concentrations in the fetal plasma. Prolonged oxygen deprivation always results in the development of a fetal shock syndrome with acidosis, increasing basal FHR and peripheral vasoconstriction. Thusfar the life saving circulatory centralisation could only be revealed indirectly by cardiotocography and micro blood sampling. As vasoconstriction of the fetal skin during stress reduces the transcutaneously measured PO_2 (tc PO_2), tc PO_2 monitoring turns out to be a practical method to discover a shock syndrome of the human fetus directly by evaluating the transcutaneous-arterial PO_2-Difference (tc-art.PO_2-D). This study was designed to elucidate the interrelations between Epi- and Norepinephrine, as mediating substances of the fetal shock syndrome, and circulatory variables, such as pH and base excess (BE).

MATERIAL AND METHODS: 21 experiments were performed by using 8 acutely instrumented ewes at term and 3 chronic preparations. Uterine blood flow was interrupted 11 times within 30 minutes after cannulating the fetal and maternal femoral artery and vein. The tcPO_2 electrode was glued on the opposite hind limb of the fetus. Uterine blood flow was stopped for 30,60 and 90 seconds, respectively, by occlusion of the descending maternal aorta (MAO). In 15 acute experiments fetal heart rate (FHR), oxygen saturation (SO_2), relative local skin perfusion(RLP) and tcPO_2 were monitored continuously. Blood samples were taken at control and at 33 minutes for pH,PO_2,PCO_2,SO_2 and catecholamine measurements (Fig.1). The plasma catecholamine concentrations were estimated by radio enzymatic assay in cooperation with the Pharmacology Department of HEIDELBERG-UNIVERSITY.

	maternal aorta occlusion 30 sec $\bar{x}$ (SE) N = 3		maternal aorta occlusion 60 sec $\bar{x}$ (SE) N = 9		maternal aorta occlusion 90 sec $\bar{x}$ (SE) N = 3	
	Control	33rd min.	Control	33rd min.	Control	33rd min.
PH	7,39 (0,04)	7,36 (0.03)	7,35 (0,02)	7,24 (0,04)	7,37 (0,03)	7,08 (0,01)
PO_2 (mm Hg)	21,8 (1,9)	19,1 (0,6)	21,4 (1,1)	19,7 (1,1)	22,6 (3,1)	21,6 (2,1)
PCO_2 (mm Hg)	49,2 (6,9)	51,2 (5,5)	49,1 (1,9)	56,3 (4,0)	48,7 (2,0)	65,9 (5,7)
SO_2 (%)	60,1 (3,0)	49,9 (1,6)	52,6 (4,3)	41,8 (4,6)	56,8 (7,5)	34,5 (4,5)
Base Excess (mmol/l)	1,5 (1,4)	0,2 (1,8)	1,2 (0,9)	6,7 (1,9)	0,5 (1,4)	14,2 (1,5)
Deceleration Area	359		1572		2157	
(b · min^{-1} · min)	(166)		(265)		(204)	
tc-art.PO_2 difference (mm Hg)	7,6 (4,6)	7,6 (4,1)	7,6 (1,8)	10,78 (1,4)	7,5 (2,3)	15,9 (2,4)
Norepinephrine (ng/ml)	0,73 (0,22)	0,62 (0,24)	0,64 (0,12)	2,21 (0,58)	0,39 (0,04)	10,61 (3,33)
Epinephrine (ng/ml)	0,098 (0,04)	0,071 (0,02)	0,064 (0,02)	1,176 (0,73)	0,044 (0,02)	11,96 (7,13)

RESULTS: The transcutaneous-arterial PO_2-difference. At control and after the experiment at 33 minutes exhibited a logarithmic relationship with the NE and E concentrations of the fetal blood.(tc-art. PO_2-D=9.3+2.5 lnNE, r=0.64,$2\alpha < 0.001$; tc-art.PO_2-D=120+1.6 lnE, r= 0.61; $2\alpha < 0.001$, n=15). The skin blood flow (RLP) was investiga-

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ted in 9 of 15 cases and decreased with increasing concentrations of NE and E in the 33rd min: RLP % control=89.0-15.1 lnNE, r= -9.97, $2\alpha < 0.0001$;RLP % control=71.7 -8.6 ln E, r= -0.94, $2\alpha < 0.0001$. The deceleration area (DA) during the entire experiment was evaluated in 13 cases and expressed in $b \cdot min^{-1} \cdot min$. The DA, increased exponentially with the severity of hypoxia and with rising NE concentrations: $DA = 0.41 \cdot e^{0.001 \cdot NE}$; r = 0.76 (n = 13). The change of the base excess (Δ BE) throughout the experiments, as a measure of the metabolic component of acidosis during hypoxia, increases with increasing release of NE. Both parameters exhibited a linear relationship: BE = 0,69 NE - 1.4, r=0.84, $2\alpha < 0.001$ (n = 15). The blood pH correlated logarithmically with NE as well as E concentrations but for E severer hypoxia was mandatory to attain equivalent plasma concentrations. NE was the more sensitive parameter. Even minor changes of the pH below 7.4 were accompanied by rising NE concentrations whereas E significantly increased after severe hypoxic episodes with pH values below 7.20. The ratio of NE and E decreased from about 10 at a pH of 7.35 to a ratio of one at a pH of 7.0.

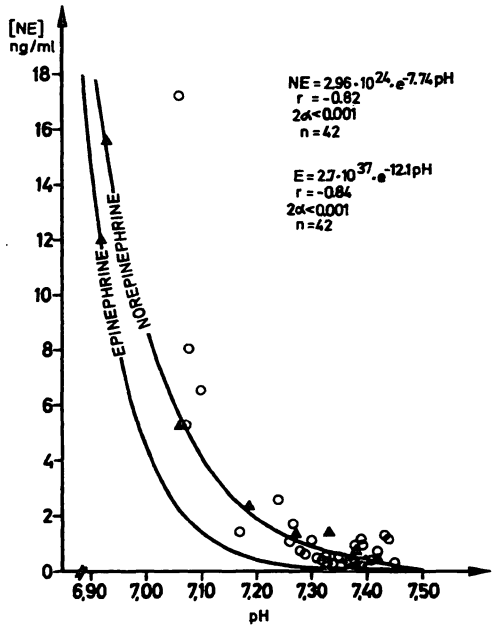

Fig. 2: Norepinephrine (NE) and Epinephrine (E) concentrations and blood pH-values. pH-values were estimated at control and after the experiment at 33 minutes and plotted against the respective NE-concentrations in the fetal plasma. Circles (O) represent acute and triangles (▲) chronic preparations. Both parameters correlate well ($2\alpha < 0.001$). Decreasing blood pH-values of the fetus are accompanied by exponentially increasing NE concentrations. Particularly interesting is the fact that the NE release is hardly different in chronic and acute preparations. To evoid confusion, just the calculated regressionline of E was drawn without any symbols.

CONCLUSIONS: 1.) Repetitive hypoxic episodes produce increasing plasma NE and E concentrations in the fetus. The ultimate concentrations depend on the duration of hypoxia. 2.) High plasma NE and E concentrations exert a strong influence on the $tcPO_2$ and generate a considerable transcutaneous-arterial PO_2-difference. 3.) Large deceleration areas are accompanied by high concentrations of E and NE. 4.) Decreasing blood pH values of the fetus result in exponentially increasing E and NE concentrations and low $tcPO_2$ readings. Therefore the $tcPO_2$ measurement is valid for early detection of a developing acidosis, which indicates an impending fetal shock syndrome.

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